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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,804	03/13/2007	Meilin Liu	IMCLON 3.3-005	1328

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EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	**PAPER NUMBER**
1647	

NOTIFICATION DATE	DELIVERY MODE
04/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/593,804	LIU ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-41* is/are pending in the application.

4a) Of the above claim(s) *14-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/10/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. In the amendment filed on 09/25/2008 Applicant cancelled claim 8, and amended claim 1-5 and 11. Claims 1-7 and 9-41 are pending. Claims 14-41 remain withdrawn. Claims 1-7 and 9-13 are currently examined.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. As evidenced in the Remarks filed 09/25/2008 Applicant, the Sequences 2, 4, 6, 8, 10, 12, 14, and 16, claimed in the PCT Application were disclosed in the provisional Applications. Consequently, the priority benefit of the provisional application 60/554555 and 60/624264 has been granted.

Specification

3. The abstract of the disclosure is objected to because it is not pertinent to the Application. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use

thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

Withdrawn claim rejections

4. The rejections of claims 1 and 8-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Jakobovits et al. (U.S. Pat. No. 6,235,883) is withdrawn in view of the amendments to the claims.

Maintained and new claim rejections necessitated by amendment

Claim Rejections - 35 USC § 112

5. Claims 1-5 and 9-13 remain and claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for any antibody that does not contain the SEQ ID NOs 2, 4 and 6 comprised within SEQ ID NO 8 **and** SEQ ID NOs 10, 12 and 14 comprised within SEQ ID NO 16 (i.e. IMC-11F8 antibody). The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to: an isolated human antibody or antibody **fragment** comprising complementarity determining regions selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16. The antibody or antibody fragment binds selectively to EGFR and might inhibit binding of EGFR to a ligand of EGFR or neutralizes EGFR. The antibody fragment is selected from the group consisting of a single chain antibody, a Fab, a single chain Fv, a diabody, and a triabody. Also claimed is a conjugate of the antibody or antibody fragment to an anti-neoplastic agent, a target moiety or a reporter moiety.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the specification discloses a full antibody (IMC-11F8-containing SEQ ID NO 8 and SEQ ID NO 16) that has all the functional characteristics claimed ([0054]). Other than this any fragment that might contain portions of it were not described as having functionality. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the

description of one antibody (IMC-11F8) is not adequate written description of an entire genus of functionally equivalent fragments.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

Therefore, only the human that has the variable heavy chain of SEQ ID NO 8 and the variable light chain consisting of the sequence of SEQ ID NO: 16 but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

On page 8 of the Remarks Applicant argues that, the amended claims are sufficiently described in the specification so as to reasonably convey that the inventors had possession of the claimed invention. The arguments were carefully considered but not found persuasive because as iterated, supra, with the exception of the antibody IMC-11F8, the fragments containing less than the polypeptides of SEQ ID NOs 8 and 16 <u>are</u> structurally and functionally described.

6. On page 9 of the Remarks Applicant argues that they have sufficiently described possible conjugation partners in the specification. The arguments were carefully

considered and found persuasive. Claims 1-7 and 9-13 remain rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling only for an isolated antibody comprising **all** the six CDRs (3 CDRs of a heavy chain amino acid sequence **and** 3 CDRs of a light chain amino acid sequence) and which binds to EGRF (i.e. antibody IMC-F11F8), does not reasonably provide enablement for antibodies that have any of the above mentioned sequences missing or fragments of the antibodies and without the knowledge whether it binds to a specific antigen such as EGFR, for the reasons of record.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

This rejection encompasses two distinct issues, which will be addressed in turn: Enablement is not commensurate in scope with claims to make and use any isolated

protein antibody that does not contains all six immunoglobulin variable domains CDRs from immunoglobulin heavy and light chains.

The specification discloses the IMC-11F8 antibody that binds specifically to the extracellular domain of EGFR receptor (p.12). The specification does not teach how to make and use any isolated protein mentioned above that lacks any or all six immunoglobulin variable domains CDRs from immunoglobulin heavy and light chains and has the properties of the IMC-11F8.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRS which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl. Acad. Sci. USA 79: 1979, 1982), which teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the

loss of antigen-binding function. Kobrin et al (J Immunology 146: 2017-2020, 1991) teach that a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine binding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular). Barrios et al (J Molecular Recognition 17: 332-338, 2004) teach the length of the antibody heavy chain CDR3 is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and heavy chains (framework region) is important in maintaining their required conformation for binding and in vivo activity. Given the insufficient guidance and in vivo working examples, it is unpredictable which undisclosed isolate protein comprising only one CDR (claim 1) still binds specifically to EGFR ectodomain and has the properties claimed. Accordingly, an undue amount of experimentation would be required to determine how to make and use the claimed invention with an antibody having less then 6 CDRs within the correct frame.

On page 10-11 of the Remarks Applicant argues that the specification would enable a person of ordinary skill in the art to obtain the antibody fragments without due experimentation. The arguments were carefully considered but not found persuasive because, as presented, supra, antibody fragments are insufficiently described structurally and functionally. This would put the person of ordinary skill in the art in the unenviable position to try and make a vast amount of fragments and then functionally test all these, and it is considered that the amount of experimentation is still undue.

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/

Primary Examiner, Art Unit 1647